Notice of Allowability	Application No.	Applicant(s)	
	09/879,572	RAMSINGH ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *4/5/07*.

2. ☒ The allowed claim(s) is/are *1,6-15,17,18,21,22,24-28,30-36,54 and 56-73*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☒ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Sandy Livnat on May 9, 2007. **All claims are rejoined and the restriction requirement between claimed inventions is withdrawn.**

The application has been amended as follows:

IN THE SPECIFICATION:

At page 7, line 4, text has been inserted, see attached.

IN THE CLAIMS:

Claims 13, 28, 67 and 70 have been amended; see attached claim listing.

Examiner's Comment

2. The specification was amended in order to provide proper antecedent basis for the claims as originally filed (see 37 CFR 1.75(d)(1) and MPEP § 608.01(o)).

Claims 13 and 28 were amended to clarify the position of the insertion of the nucleic acid. The codon that begins at nucleotide position 744 is the first codon of the viral polypeptide which begins with VP4. Nucleotides 744-746 represent the first codon of the viral polypeptide which begins with VP4. Claim 67 was amended to clarify the claim language. Claim 70 was amended to delete "nonhuman", since the term is not literally supported in the specification.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specifically, Sadia S. Halim's address has been altered by indicating an apartment number without initialing and dating by the alteration. Note that the filing of an application data sheet with the corrected information will be accepted in lieu of a new declaration/oath.

Conclusion

4. Claims 1, 6-15, 17, 18, 21, 22, 24-28, 30-36, 54 and 56-73 as amended are allowable.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 5/9/07
STACY B. CHEN
PRIMARY EXAMINER

In the specification, page 7, line 4, insert the following:

--The present invention is directed to a recombinant attenuated coxsackievirus B4 virion, such as JVB/CB4P, which is engineered to contain a heterologous nucleic acid within the open reading frame of its genome, wherein the heterologous nucleic acid encodes a heterologous polypeptide which is expressed by the virion. The heterologous nucleic acid is preferably in the P1 region of the genome. The heterologous nucleic acid is preferably in frame with the coding region such that the heterologous polypeptide is expressed as a fusion of a viral capsid protein, preferably expressed within an immunogenic region of the viral capsid protein, preferably VP1. The heterologous nucleic acid is preferably expressed as an internal fusion of VP1.

In the above recombinant virion, the immunogenic region of VP1 preferably contains B-cell epitopes, T-cell epitopes, or both. The heterologous polypeptide is preferably expressed within the viral capsid protein VP1 at a position which corresponds to the DE loop, preferably directly downstream of codon 129 of VP1 coding sequences. Preferably, the heterologous nucleic acid replaces nucleic acid sequences corresponding to VP1 codons 130-137.

In another embodiment of the recombinant virion, the heterologous nucleic acid is inserted in frame and directly upstream of sequences which encode VP4, preferably as an amino-terminal fusion of the viral polyprotein which may be directly after the first codon of the viral polyprotein. The insert may be from about 60 to about 360 nucleotides in length. In one embodiment, the amino-terminal fusion is susceptible to cleavage from the viral polyprotein by a viral protease.

The invention is also directed to a nucleic acid comprising the complete genome of a recombinant attenuated coxsackievirus B4 virion, such as JVB/CB4-P, which is engineered to contain a heterologous nucleic acid within the open reading frame of its genome, wherein the heterologous nucleic acid encodes a heterologous polypeptide which is expressed by the virion. This nucleic acid may be an infectious cDNA or infectious RNA of the viral genome. The heterologous nucleic acid is preferably inserted into the P1 region of the genome, more

preferably into the coding region of VP1, such as into sequences which encode the DE loop of VP1. The heterologous nucleic acid insert may be directly downstream of codon 129 of VP1 coding sequences and replace codons 130-137 of VP1 coding sequences.

In another embodiment of the nucleic acid, the heterologous nucleic acid is inserted in frame and directly upstream of sequences which encode VP4, preferably directly after the first codon encoding VP4. The inserted heterologous nucleic acid may be from about 25 nucleotides to about 39 nucleotides in length. The insert preferably results in an antigenic polypeptide such as viral polypeptide or a fragment thereof when expressed in the context of the coxsackievirus B4 genome. The insert may further encode a T cell epitope, a B cell epitope, or both a T cell and a B cell epitope. The insert may encode a bacterial pathogen polypeptide or a fragment thereof. In a preferred embodiment, the insert encodes an HIV polypeptide or a fragment thereof, for example, HIV p24 or a fragment thereof.

The present invention is also directed to a method for inducing an immune response to a polypeptide in an individual, comprising: (a) providing a recombinant attenuated coxsackievirus B4 virion which is engineered to contain a heterologous nucleic acid within the open reading frame of its genome, wherein the heterologous nucleic acid encodes a heterologous polypeptide which is expressed by the virion; and (b) administering the recombinant attenuated coxsackievirus B4 virion to the individual under conditions appropriate for infection. In this method, the recombinant attenuated coxsackievirus B4 virion is formulated with a physiologically acceptable carrier. Preferably, the heterologous nucleic acid is expressed in the recombinant attenuated coxsackievirus B4 virion as an internal fusion of VP1 such that the heterologous nucleic acid is expressed within an immunogenic region of VP1. The immune response induced may comprise the generation of a cytotoxic T-cell response, a T helper cell response, B cell response, or any combination thereof.

In the above method, the heterologous nucleic acid is preferably expressed as an amino-terminal fusion of the viral polyprotein, which fusion may be susceptible to cleavage from the viral polyprotein by a viral protease. In the above method, the heterologous nucleic acid may further

encode a T-cell epitope. In the above method for inducing an immune response, the heterologous polypeptide may be a polypeptide or fragment thereof from a pathogen of the individual. The immune response which is generated in the individual preferably prevents or inhibits disease progression in the individual. The polypeptide is preferably a viral polypeptide, such as an HIV polypeptide, preferably HIV polypeptide p24 or a fragment thereof. In the above method, the individual is an animal or a human who may be immunocompromised.

The present invention provides a method for inducing an immune response in an individual which is protective against coxsackievirus B4, comprising: (a) providing a recombinant coxsackie virion of the invention; and (b) administering the virion to the individual under conditions appropriate for infection.

Also included is a method for delivering a polypeptide to an individual, comprising:

(a) providing a recombinant attenuated coxsackievirus B4 virion which is engineered to contain a heterologous nucleic acid within the open reading frame of its genome, wherein the heterologous nucleic acid encodes a heterologous polypeptide which is expressed by the virion, wherein the heterologous nucleic acid is expressed as an amino-terminal fusion of viral polyprotein wherein the amino-terminal fusion is susceptible to cleavage from the viral polyprotein by a viral protease; and

(b) administering the recombinant attenuated coxsackievirus B4 virion of step (a) to the individual under conditions appropriate for infection.--

LISTING OF CLAIMS WITH EXAMINER'S AMENDMENT

1. (previously presented) A recombinant attenuated coxsackievirus B4 virion which is engineered to contain a heterologous non-coxsackievirus nucleic acid inserted within the P1 region of the open reading frame of its genome which inserted nucleic acid encodes a non-coxsackievirus heterologous polypeptide which is fused to a capsid protein of the virion.

2-5. (canceled)

6. (currently amended) The recombinant [[CB4-P]] virion of Claim 1 [[3]] wherein the heterologous polypeptide is situated within an immunogenic region of the viral capsid protein.

7. (currently amended) The recombinant [[CB4-P]] virion of Claim 6 wherein the heterologous nucleic acid is expressed as an internal fusion of VP1.

8. (currently amended) The recombinant [[CB4-P]] virion of Claim 6 wherein the viral capsid protein is VP1.

9. (currently amended) The recombinant [[CB4-P]] virion of Claim 8 wherein the immunogenic region of VP1 comprises a B-cell epitope, a T-cell epitope, or both a B cell epitope and a T cell epitope.

10. (currently amended) The recombinant [[CB4-P]] virion of Claim 8 wherein the heterologous polypeptide is situated within VP1 at a position which corresponds to the DE loop.

11. (currently amended) The recombinant [[CB4-P]] virion of Claim 10 wherein the heterologous nucleic acid is directly downstream of codon 129 of VP1 coding sequences.

12. (currently amended) The recombinant [[CB4-P]] virion of Claim 11 wherein the nucleic acid sequence corresponding to VP1 codons 130-135 of wild type CB4[[-P]] is deleted.

13. (currently amended) The recombinant [[CB4-P]] virion of Claim 1 [[3]] wherein the heterologous nucleic acid is inserted in-frame and directly upstream of sequences which encode VP4, or is directly 3' from the AUG codon beginning at nucleotide 744 of the CB4 RNA genome that encodes the N-terminal Met of native viral polyprotein.

14. (currently amended) The recombinant [[CB4-P]] virion of Claim 13 wherein the heterologous polypeptide is expressed as an amino-terminal fusion of the viral polyprotein.

15. (currently amended) The recombinant [[CB4-P]] virion of Claim 14 wherein the amino-terminal fusion is susceptible to cleavage from the viral polyprotein by a viral protease.

16. (canceled)

17. (currently amended) The recombinant [[CB4-P]] virion of Claim 14 wherein the length of inserted heterologous nucleic acid is from about 60 to about 360 nucleotides.

18. (previously presented) A nucleic acid comprising the complete genome of a recombinant attenuated coxsackievirus B4 virion which is engineered to contain a heterologous non-coxsackievirus nucleic acid insert which is inserted within the P1 region of the open reading frame of its genome, wherein the insert encodes a non-coxsackievirus heterologous polypeptide which in the virion is fused to a capsid protein.

19-20. (canceled)

21. (currently amended) The nucleic acid of Claim 18 [[20]] which is an infectious cDNA of the CB4[[-P]] genome.

22. (currently amended) The nucleic acid of Claim 18 [[20]] which is an infectious RNA of the CB4[[-P]] genome

23. (canceled)

24. (currently amended) The nucleic acid of Claim 18 [[20]] wherein the insert is in the coding region of VP1.

25. (previously presented) The nucleic acid of Claim 24 wherein the insert is in sequences which encode the DE loop of VP1.

26. (previously presented) The nucleic acid of Claim 25 wherein the insert is directly downstream of codon 129 of the VP1 coding sequences.

27. (currently amended) The nucleic acid of Claim 26 wherein the nucleic acid sequence corresponding to VP1 codons 130-135 of wild type CB4[[-P]] is deleted.

28. (currently amended) The nucleic acid of Claim 18 [[20]] wherein the insert is in-frame and directly upstream of sequences which encode VP4, or is directly 3' from the AUG codon, at nucleotide positions 744-746 of the CB4 RNA genome, that encodes the N-terminal Met of native viral polyprotein.

29. (canceled)

30. (previously presented) The nucleic acid of Claim 26 wherein the insert is from about 25 nucleotides to about 39 nucleotides in length.

31. (currently amended) The nucleic acid of Claim 26 wherein the polypeptide is immunogenic when fused to [[CB4-P]] the VP1 capsid protein.

32. (previously presented) The nucleic acid of Claim 31 wherein the insert encodes a T cell epitope, a B cell epitope, or both a T cell epitope and a B cell epitope.

33. (previously presented) The nucleic acid of Claim 31 wherein the insert encodes a viral polypeptide or a peptide epitope thereof.

34. (previously presented) The nucleic acid of Claim 31 wherein the insert encodes a polypeptide or a peptide epitope of a bacterial pathogen.

35. (previously presented) The nucleic acid of Claim 31 wherein the insert encodes an HIV polypeptide or a peptide epitope thereof.

36. (previously presented) The nucleic acid of Claim 35 wherein the insert encodes HIV p24 or a peptide epitope thereof.

37-53. (canceled)

54. (previously presented) A method for inducing an immune response to a polypeptide in a subject, comprising administering the recombinant attenuated coxsackievirus B4 virion of claim 1 to the subject under conditions appropriate for infection by the virion.

55. (canceled)

56. (previously presented) The method of Claim 54 wherein the recombinant attenuated coxsackievirus B4 virion is formulated with a physiologically acceptable carrier.

57. (previously presented) The method of Claim 54 wherein the immune response comprises the generation of a cytotoxic T-cell response, a T helper cell response, a B cell response, or any combination thereof.

58. (previously presented) The method of Claim 54 wherein the heterologous nucleic acid encodes a T-cell epitope.

59. (currently amended) A method for inducing an immune response to a polypeptide in a subject, comprising administering a recombinant attenuated CB4[[-P]] virion comprising the nucleic acid of claim 32 to the subject under conditions appropriate for infection by the virion.

60. (currently amended) A method for inducing an immune response to a polypeptide in a subject, comprising administering the recombinant attenuated CB4[[-P]] virion of claim 7 to the subject under conditions appropriate for infection by the virion.

61. (currently amended) A method for inducing an immune response to a polypeptide in a subject, comprising administering the recombinant attenuated CB4[[-P]] virion of claim 14 to the subject under conditions appropriate for infection by the virion.

62. (currently amended) A method for inducing an immune response to a polypeptide in a subject, comprising administering the recombinant attenuated CB4[[-P]] virion of claim 15 to the subject under conditions appropriate for infection by the virion.

63. (currently amended) A method for inducing an immune response to a bacterial polypeptide in a subject, comprising administering a recombinant attenuated CB4[[-P]] virion comprising the heterologous nucleic acid of claim 34 to the subject under conditions appropriate for infection by the virion.

64. (previously presented) The method of Claim 63 wherein the immune response prevents or inhibits progression of a disease in the subject caused by bacteria comprising the heterologous bacterial polypeptide.

65. (currently amended) A method for inducing an immune response to a viral polypeptide in a subject, comprising administering a recombinant attenuated CB4[[-P]] virion comprising the nucleic acid of claim 33 to the subject under conditions appropriate for infection by the virion.

66. (previously presented) The method of Claim 65 wherein the immune response prevents or inhibits progression of a disease in the subject caused by a virus comprising the heterologous viral polypeptide, wherein the heterologous viral polypeptide comprises a viral epitope.

67. (currently amended) The method of Claim 65 wherein the viral polypeptide is an HIV polypeptide or a peptide epitope thereof.

68. (previously presented) The method of Claim 67 wherein the HIV polypeptide is p24 or a peptide epitope thereof.

69. (previously presented) The method of Claim 54 wherein the subject is a human.

70. (currently amended) The method of Claim 54 wherein the subject is an animal.

71. (previously presented) The method of Claim 54 wherein the subject is immunocompromised.

72. (currently amended) A method for delivering a polypeptide to a subject, comprising administering to the subject, under conditions appropriate for infection, a recombinant attenuated coxsackievirus B4 virion which is engineered to comprise a non-coxsackievirus heterologous nucleic acid insert that is inserted within the open reading frame of the ~~coxsackievirus~~ CB4 genome, which insert encodes the polypeptide being delivered, which polypeptide is

(i) a heterologous non-coxsackievirus polypeptide fused to a capsid protein of the virion,

(ii) expressed as an amino-terminal fusion with ~~coxsackievirus~~ CB4 viral polyprotein; and

(iii) susceptible to cleavage by a viral protease that cleaves the heterologous polypeptide from the viral polyprotein,

thereby delivering the polypeptide.

73. (previously presented) A recombinant attenuated coxsackievirus B4 virion consisting of a coxsackievirus B4 genome and a non-coxsackievirus heterologous nucleic acid inserted within the P1 region of the open reading frame of the genome, which inserted nucleic acid encodes a heterologous polypeptide which is fused to a capsid protein of the virion.

74 -78. (canceled)

(i) a heterologous non-coxsackievirus polypeptide fused to a capsid protein of the virion,

(ii) expressed as an amino-terminal fusion with ~~coxsackievirus~~ CB4 viral polyprotein; and

(iii) susceptible to cleavage by a viral protease that cleaves the heterologous polypeptide from the viral polyprotein,

thereby delivering the polypeptide.

73. (previously presented) A recombinant attenuated coxsackievirus B4 virion consisting of a coxsackievirus B4 genome and a non-coxsackievirus heterologous nucleic acid inserted within the P1 region of the open reading frame of the genome, which inserted nucleic acid encodes a heterologous polypeptide which is fused to a capsid protein of the virion.

74 -78. (canceled)